Component A, purified from a commercially supplied sample, enhances glucose uptake in differentiated 3T3-L1 cells, and the activity is not dependent on the presence of insulin. It is, however, dependent on the activity of PI-3 kinase, confirming that the glucose uptake is mediated via the insulin signaling pathway. The ability of 16 μg/ml concentrations of Component A to enhance glucose uptake at various insulin concentrations is shown in FIG. 4.

In the assay, 3T3-L1 pre-adipocytes were induced to differentiate into adipocyte morphology using standard protocols. Five days after induction, the cells were treated with 16 μg/ml of Component A in the presence of various levels of insulin for 30 minutes. Glucose uptake was measured using ^{14}C glucose as label. As shown, 16 μg/ml of Component A alone effects uptake at approximately the level shown by 20 μM concentrations of insulin in the absence of this concentration of Component A.

EXAMPLE 4

Additional Compounds Related to TER3935

An additional compound with a structure regioisomeric to that of TER3935, TER16998, was isolated by preparative reverse-phase chromatography from the reaction mixture produced by the synthetic scheme shown in FIG. 5. Spectral data confirm that the isolated compound was of the formula shown in FIG. 2D.

TER16998 activates the insulin receptor kinase directly, enhances autophosphorylation and substrate phosphorylation mediated through the insulin receptor, potentiates glucose transport and lowers blood glucose in the db/db mouse model of diabetes. These results were obtained as follows:

The assay described in Example 1, paragraph A, was conducted with a control lacking any additions, in the presence of insulin alone at 1 nM, in the presence of TER16998 at 2 μM and in the presence of a combination of these components at the stated concentrations. As shown in FIG. 6, TER16998 alone is able to activate autophosphorylation of the receptor at this concentration, as well as to potentiate the effect of insulin.

In addition, in an assay for glucose uptake by 3T3-L1 adipocytes, described in Example 3, TER16998 produced an acute effect sensitizing the cells to insulin. This was inhibited, as expected, by 5 μM wortmannin which inhibits PI-3 kinase, confiring that TER16998 exerts its effect through the insulin-signaling pathway. These results are shown in FIG. 7. As shown, 40 μM of TER16998 potentiates the effect of insulin at a range of concentrations.

Significantly, TER16998 was not able to stimulate the phosphorylation activity of epidermal growth factor receptor in an EGF receptor kinase assay.

The effect of TER16998, of Component A, and of insulin on the distribution of the Glut4 transporter in 3T3-L1 adipocytes was determined by incubating the cells for 15 minutes with insulin or one of these compounds, after which the cells were fixed and stained with an anti-Glut4 antibody followed by FITC-conjugated secondary antibody. The results were visualized under a fluorescent microscope. The results showed that insulin and Component A produce a dramatic redistribution of Glut4 to the membrane surfaces whereas in untreated cells a diffuse pattern is obtained. TER16998 has a similar effect but less dramatic than that of insulin or Component A.

EXAMPLE 5

Effect of TER16998 in Diabetic Mice

Mice which are standard models of Type II diabetes, db/db mice, were administered TER16998 at 10 mg/kg and 40 mg/kg, or a vehicle as a control. FIG. 8 shows the effect of this compound on the concentration of glucose in the blood of these animals. As shown in FIG. 8, 10 mg/kg to some extent and 40 mg/kg to an appreciable extent decrease blood glucose over a period of 24 hours from the time of administration.

EXAMPLE 6

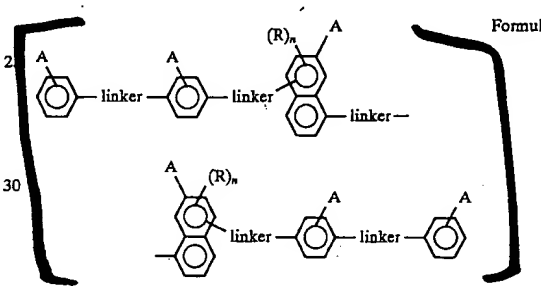
Synthesis of Analogs

Compounds TER17004 and TER17005, shown in FIG. 2E, replace certain azo-linkers of TER3935 with the corresponding amide linkers. These compounds are synthesized as shown in FIG. 9.

The resulting compounds, TER17004 and TER17005, were tested in the IR kdnase assay set forth in Example 1, paragraph A, and found to be active in this assay.

We claim:

1. A method to modulate the kinase activity of insulin receptor which method comprises contacting said insulin receptor or the kinase portion thereof with a compound of the formula



Formula (1)

wherein

each A is independently a proton-accepting substituent;

each R is independently a noninterfering substituent;

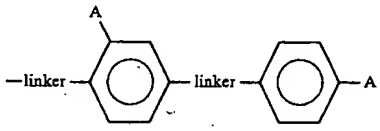
each n is independently 0, 1, or 2; and

each linker is independently an isostere of —NHCONH— or of —N=N— or of —NHCO—;

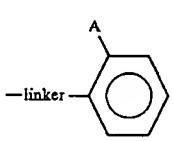
said compound provided in an amount effective to modulate said kinase activity.

2. The method of claim 1 wherein each A is independently $—SO_3X$ or —COOX wherein X is H or a cation.

3. The method of claim 1 wherein each R is independently OH or



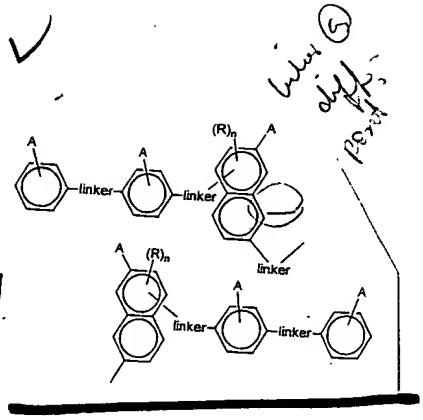
or

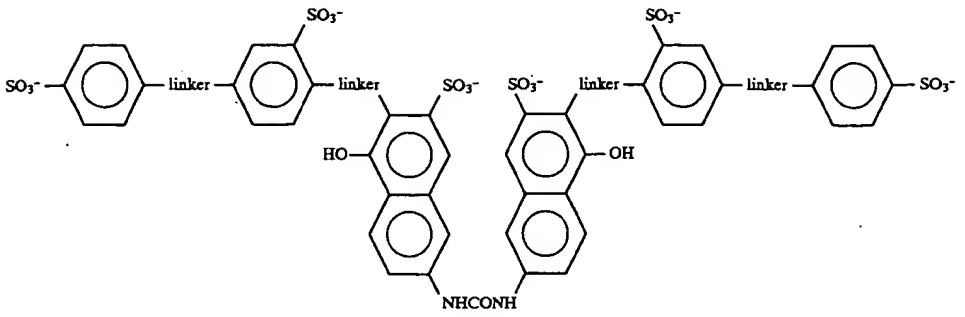


wherein linker is as defined above.

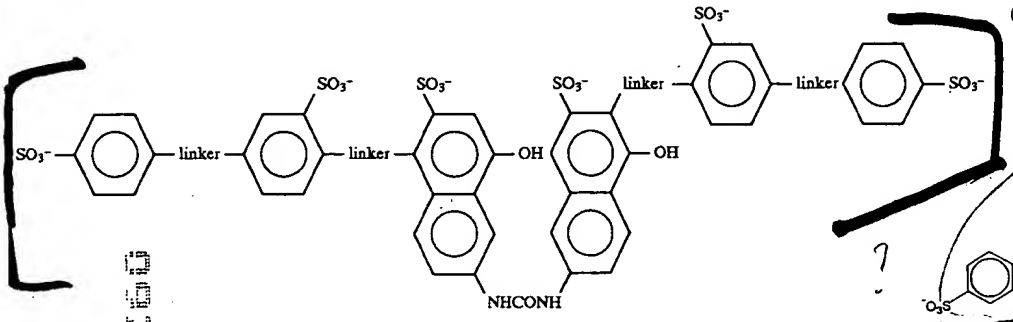
4. The method of claim 1 wherein n is 0 or 1 and each R is independently OH.

5. The method of claim 1 wherein said compound is of a formula selected from the group consisting of

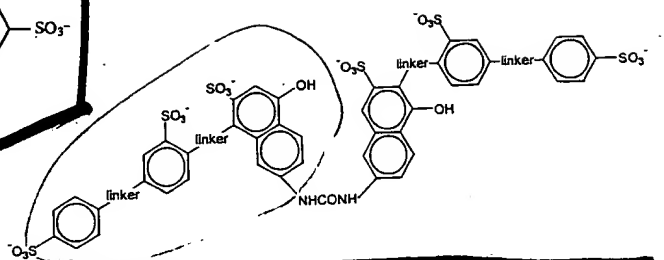




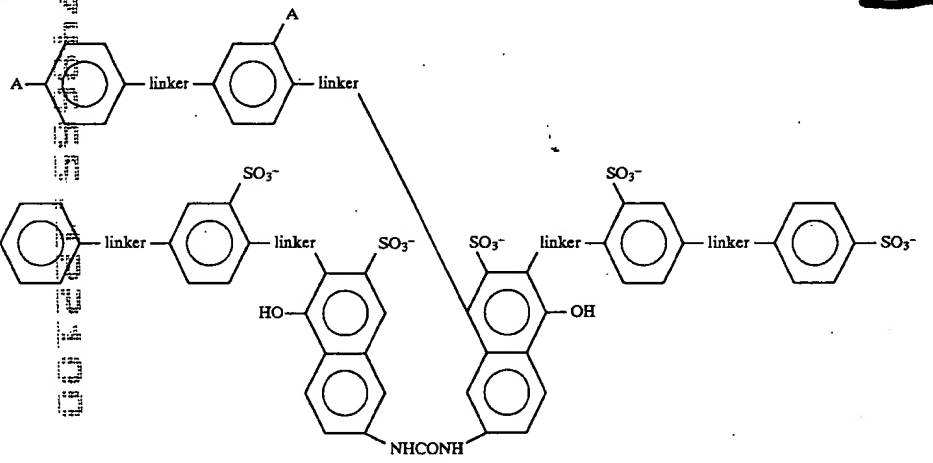
(1A)



(1B)



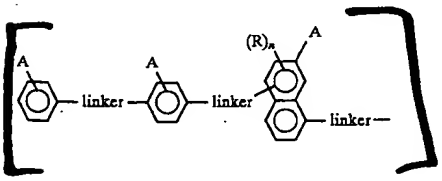
(1C)



wherein

each linker is independently either —N═N— or —NHCO—.

6. A method to potentiate the insulin activation of insulin receptor which method comprises contacting said insulin receptor or the kinase portion thereof with insulin and with a compound of the formula



Formula (1)

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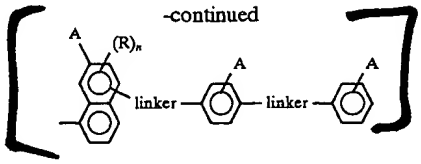


wherein

each A is independently a proton-accepting substituent;

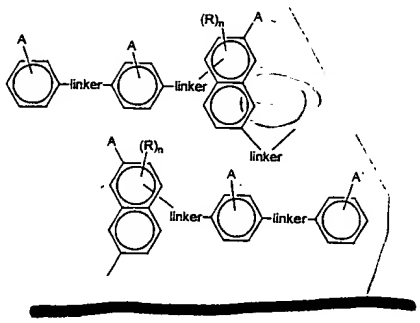
each R is independently a noninterfering substituent;

n is 0, 1, or 2; and

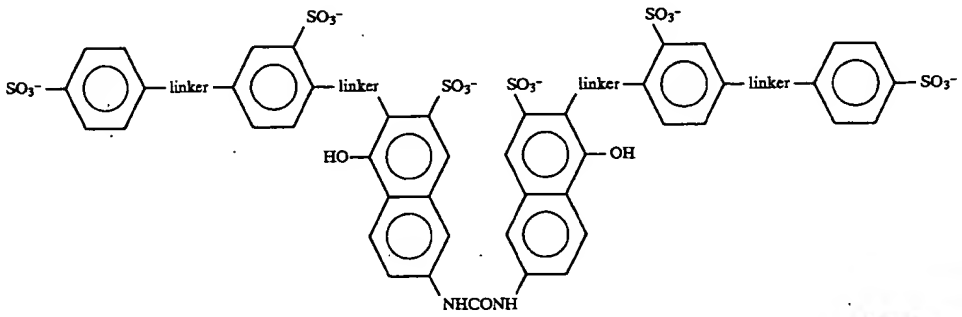
each linker is independently an isostere of —NHCONH— or of —N═N— or of —NHCO—;

said compound provided in an amount effective to potentiate said insulin activation.

7. The method of claim 6 wherein each A is independently —SO_3X or —COOX wherein X is H or a cation.



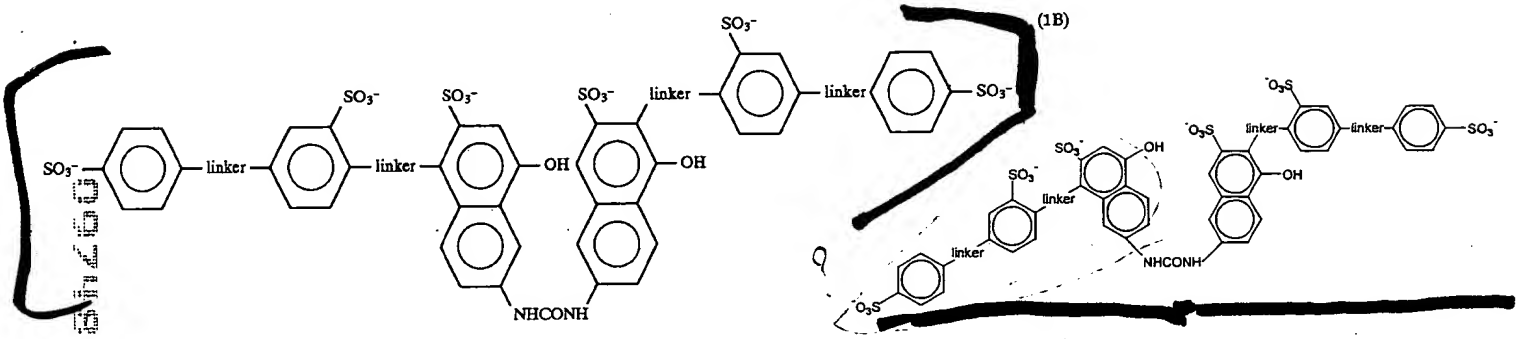
8. The method of claim 6 wherein each R is independently OH or



9. The method of claim 6 wherein n is 0 or 1 and each R is independently OH.

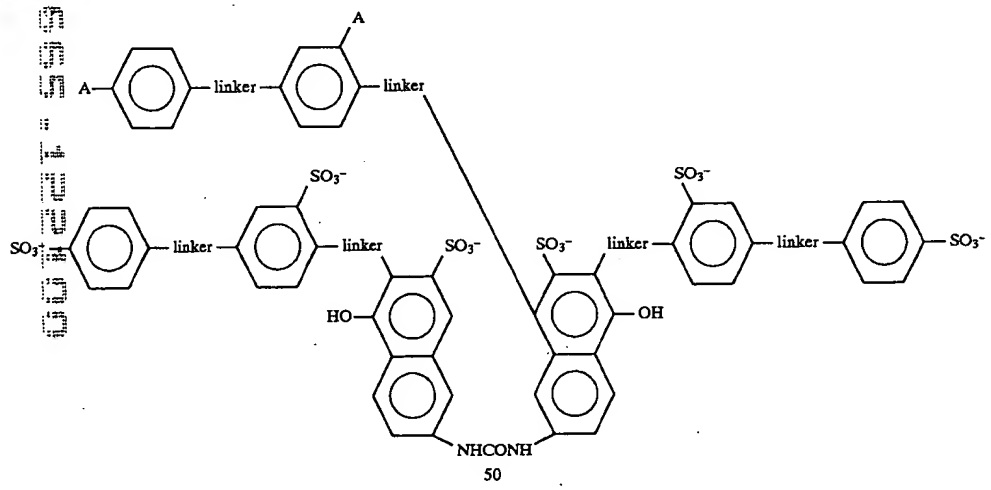
10. The method of claim 6 wherein said compound is of a formula selected from the group consisting of

(1A)



(1B)

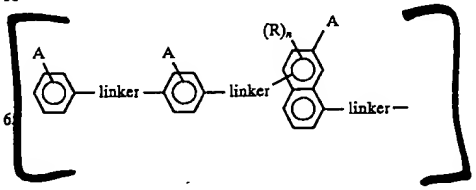
(1C)



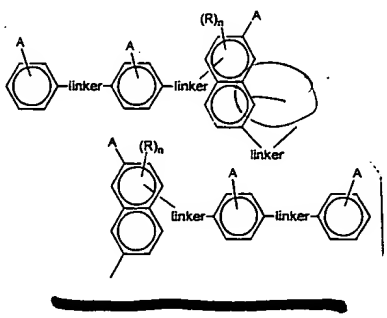
wherein

each linker is independently either —N=N— or —NHCO—.

11. A method to potentiate the stimulation by insulin of cellular glucose uptake which method comprises contacting cells displaying the insulin receptor with insulin and with a compound of the formula



Formula (1)



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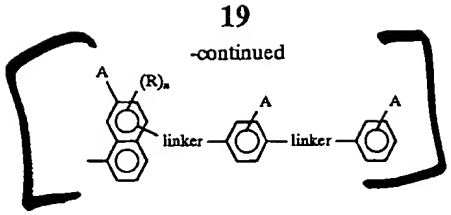


wherein

each A is independently a proton-accepting substituent;

each R is independently a noninterfering substituent;

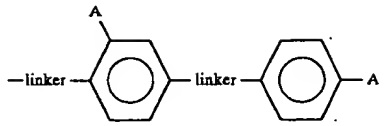
n is 0, 1, or 2; and

each linker is independently an isostere of —NHCONH— or of —N═N— or of —NHCO—;

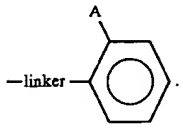
said compound provided in an amount effective to potentiate said glucose uptake.

12. The method of claim 11 wherein each A is independently $—SO_3X$ or —COOX wherein X is H or a cation.

13. The method of claim 11 wherein each R is independently OH or

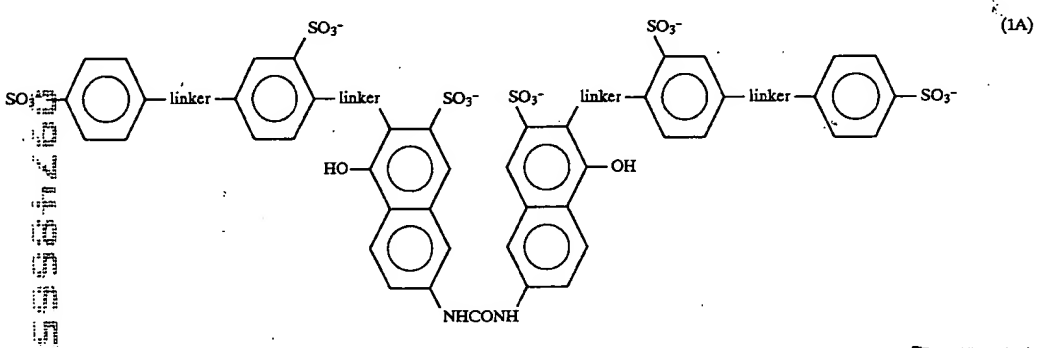


or

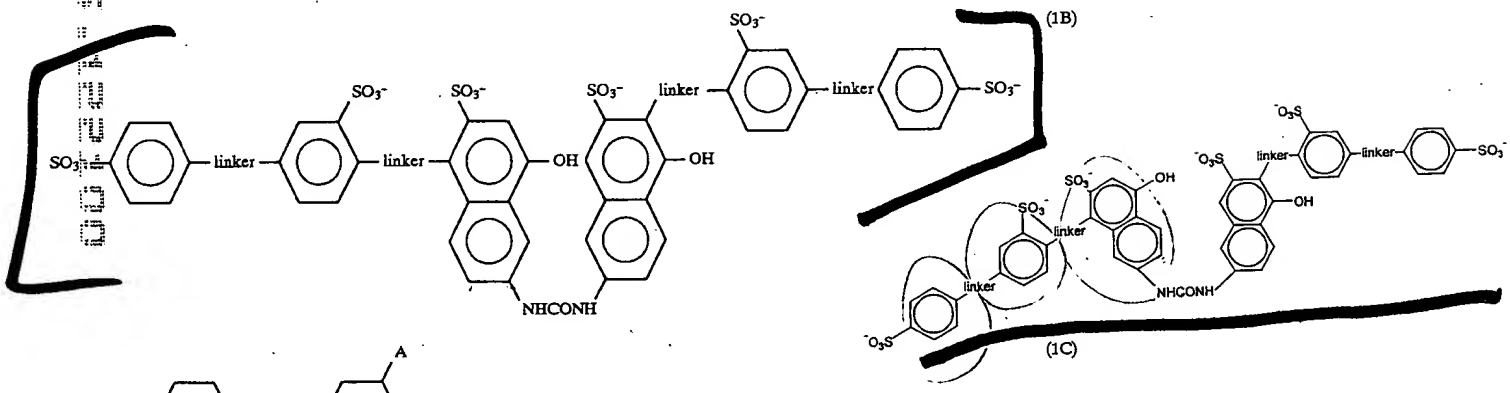


14. The method of claim 11 wherein n is 0 or 1 and each R is independently OH.

15. The method of claim 11 wherein said compound is of a formula selected from the group consisting of

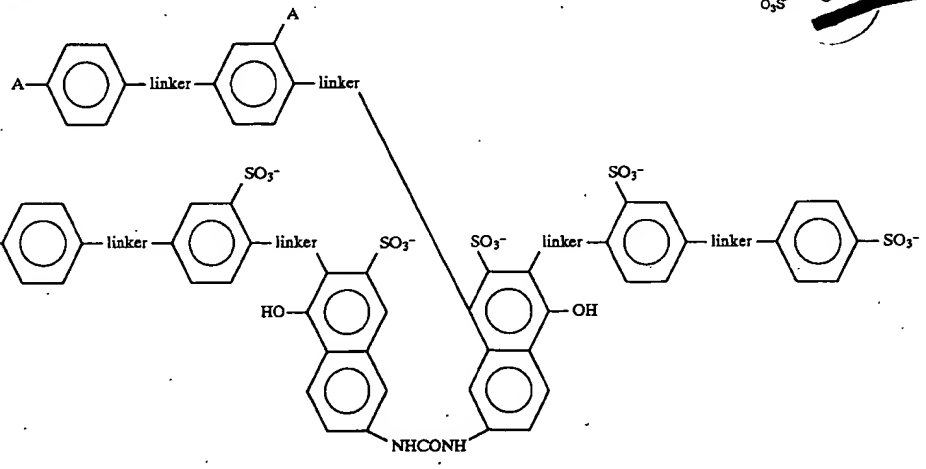


(1A)



(1B)

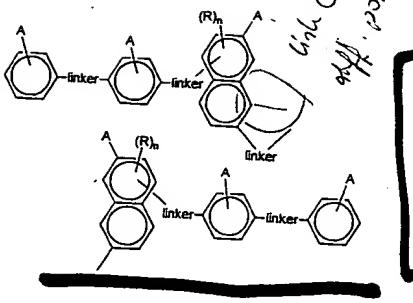
(1C)

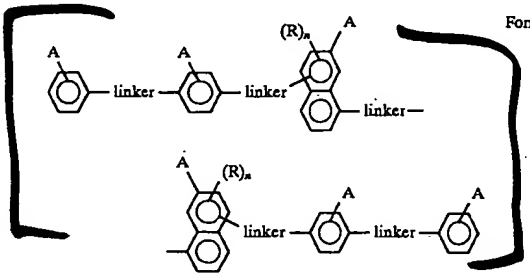


wherein

each linker is independently either —N=N— or —NHCO—.

16. A method to stimulate the uptake of glucose in cells displaying the insulin receptor which method comprises contacting said cells with a compound of the formula





Formula (1)

wherein

each A is independently a proton-accepting substituent;

each R is independently a noninterfering substituent;

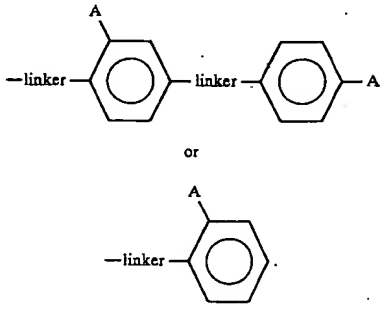
n is 0, 1, or 2; and

each linker is independently an isostere of —NHCONH— or of —N=N— or of —NHCO—;

said compound provided in an amount effective to stimulate glucose uptake.

17. The method of claim 16 wherein each A is independently —SO_3X or —COOX wherein X is H or a cation.

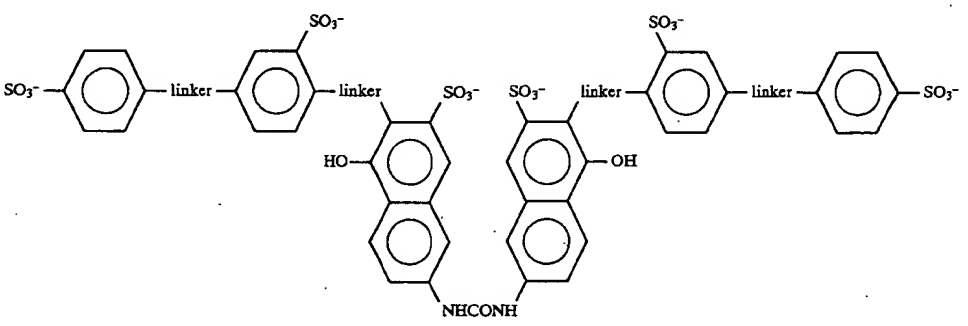
18. The method of claim 16 wherein each R is independently OH or



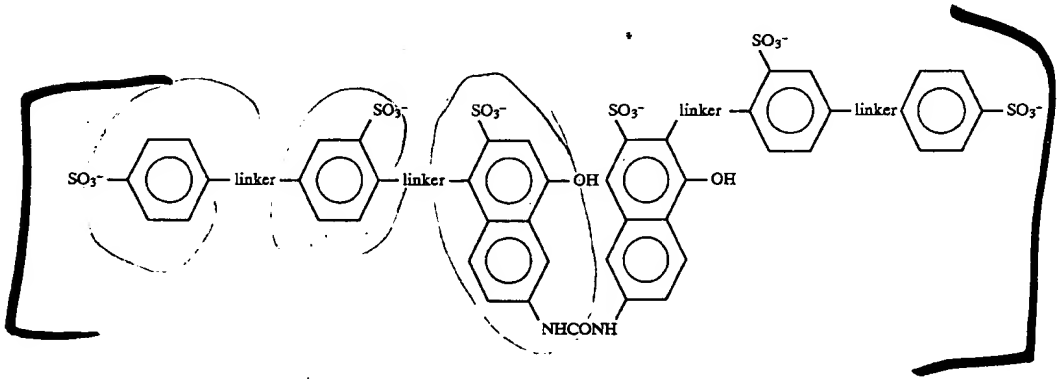
or

19. The method of claim 16 wherein n is 0 or 1 and each R is independently OH.

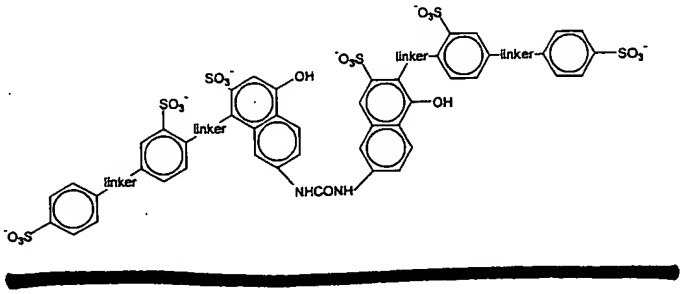
20. The method of claim 16 wherein said compound is of a formula selected from the group consisting of



(1A)



(1B)



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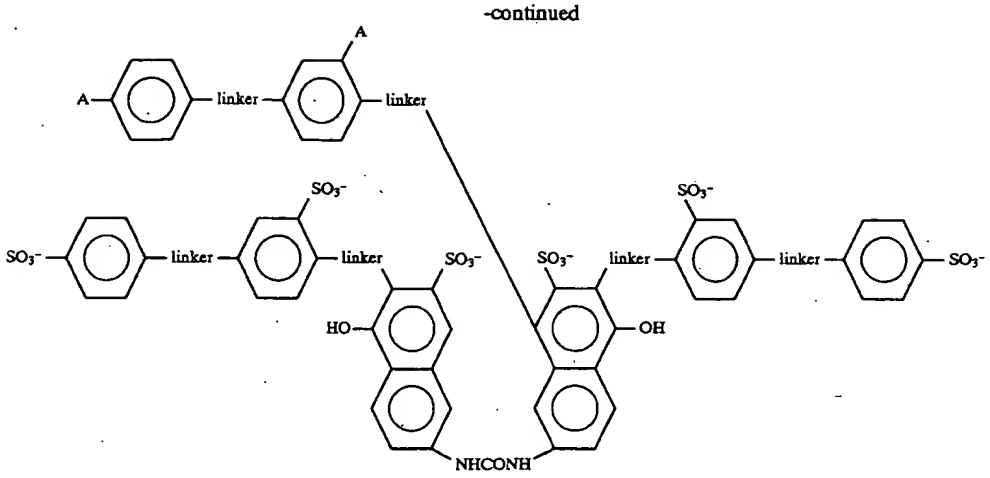
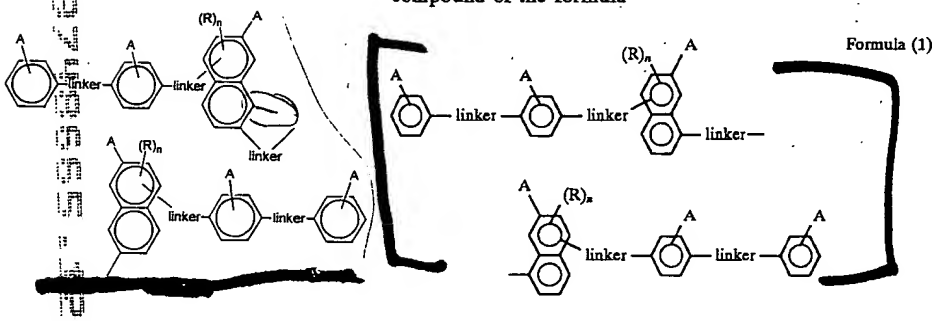


(1C)

wherein

each linker is independently either —N═N— or —NHCO—.

21. A method to lower blood glucose in a diabetic subject which method comprises administering to said subject a compound of the formula



Formula (1)

wherein

each A is independently a proton-accepting substituent;

each R is independently a noninterfering substituent;

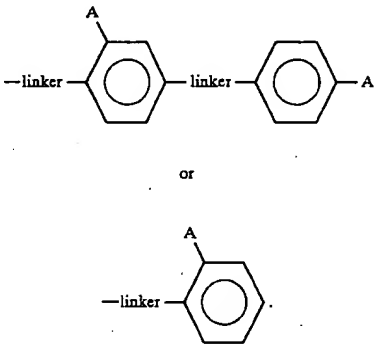
n is 0, 1, or 2; and

each linker is independently an isostere of —NHCONH— or of —N═N— or of —NHCO—;

said compound provided in an amount effective to lower blood glucose.

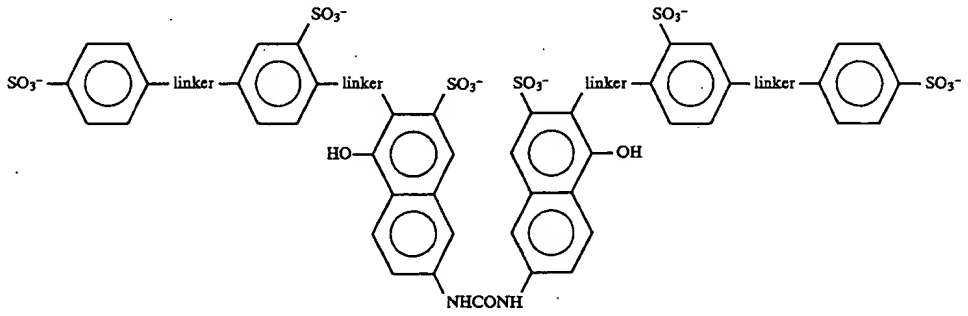
22. The method of claim 21 wherein each A is independently —SO_3X or —COOX wherein X is H or a cation.

23. The method of claim 21 wherein each R is independently OH or



24. The method of claim 21 wherein n is 0 or 1 and each R is independently OH.

25. The method of claim 21 wherein said compound is of a formula selected from the group consisting of



(1A)

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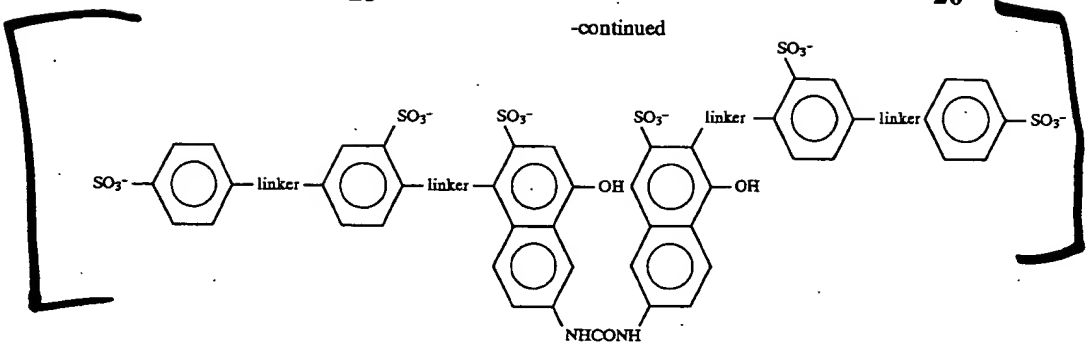
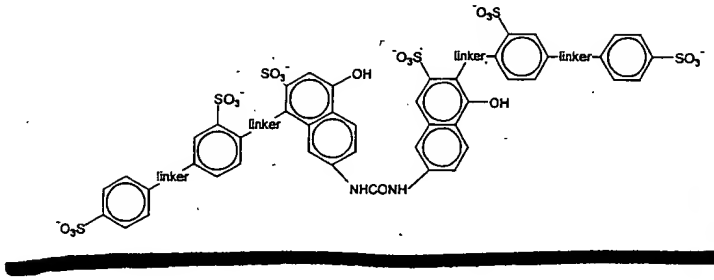
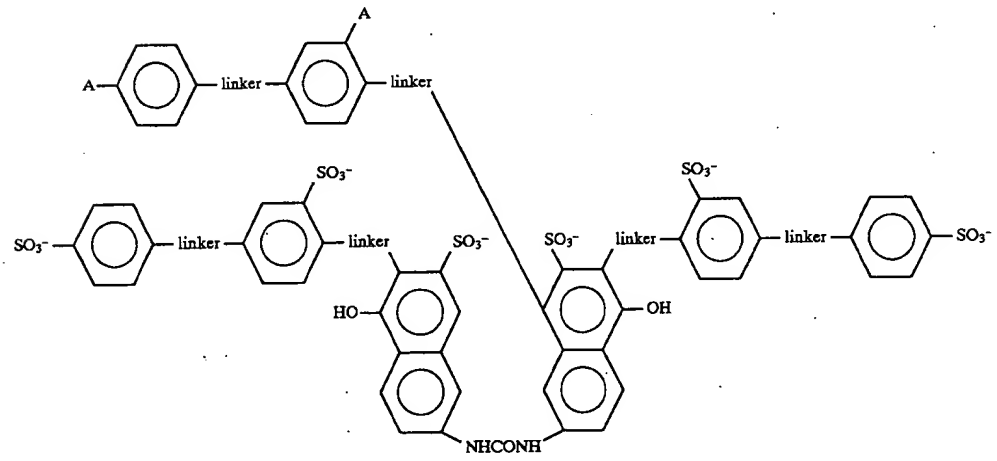


(1B)



(1C)



wherein

each linker is independently either —N=N— or —NHCO—.

* * * * *